Claims

1. A method of controlling levels/concentrations of a target moiety comprising:

(iv) introducing into a cell a product comprising at least one of each of the following modules: a targeting module, a destruction module and a replacement module;

(v) targeting the target moiety with the targeting module of the product so as to bind them together or at least bring the target moiety into close proximity with the product so that the destruction module can effect degradation of the target moiety; and

(vi) replacing the target moiety with a replacement module, the replacement module either being a modified form of the target moiety itself or a functional unit which restores normal metabolic activity of the cell.

2. A method according to claim 1 wherein the target moiety is a protein.

3. A method according to either claim 1 or 2 wherein the targeting module is selected from the group comprising a protein, polypeptide, aptamer or drug-like molecule or portions or fragments thereof.

4. A method according to any preceding claim wherein the replacement module of the product is in the form of a modified form of the target moiety itself or is in the form of a functional unit which is capable of restoring normal metabolic activity of the cell into which the product has been introduced.

5. A method according to any preceding claim wherein the destruction module acts directly or indirectly on the target moiety.

6. A method according to claim 5 wherein the destruction module acts directly on the target moiety and the destruction module comprises a proteinase.

7. A method according to claim 5 wherein the destruction module acts indirectly on the target moiety and the destruction module comprises a mutation or deletion such that it alters degradation of the target moiety.

8. A method according to any preceding claim wherein the replacement module is modified to retain beneficial attributes and to remove/delete any adverse attributes of the target moiety.

9. A product comprising at least one of each of the following modules: a targeting module as defined in claim 3, a destruction module as defined in any one of claims 5, 6 or 7 and a replacement module as defined in claim 1 or 8.

10. A product comprising a targeting module comprising a β-catenin binding domain of E-cadherin, a destruction module comprising an F-box mutated such that it is not able to bind to the phosphorylated form of β-catenin and a replacement module comprising wild type β-catenin.

11. A product comprising a targeting module comprising an inhibitor of alcohol dehydrogenase (ADH), a destruction module comprising a protease domain and a replacement module comprising a functional ADH with any protease recognition motifs removed and specific mutations to substantially reduce sensitivity to a targeting module.

12. A product comprising a targeting module comprising a PLB target motif, a destruction module comprising absence of either or both lysine 3 and/or 27 so that ubiquitinataion cannot occur together with an N-terminal domain exhibiting a destabilising N-terminal residue and a replacement module comprising a modified PLB sequence such that it is unable to inhibit Ca2+-pump activity.

13. An isolated nucleic acid comprising a modified or mutated form of a PLB nucleic acid sequence (vPLB) comprising at least one modification or mutation in the N-terminal domain and/or a deleted or mutated region that encodes a lysine residue

in the expressed protein so that at least one lysine is not expressed in the protein encoded by the modified or mutated vPLB nucleic acid sequence.

14. Nucleic acid according to claim 13 wherein the deleted or mutated region of the vPLB affects lysine 3 residue and/or lysine 27 so that either or both of lysine 3 and 27 is/are not expressed in the protein encoded by the vPLB nucleic acid.

15. Nucleic acid according to either claim 13 or 14 wherein modification or mutation of the 5' end of the nucleic acid polymer encoding PLB is such that the N-terminal domain of the protein comprises replacement of the region encoding a methionine with an unstructured linker sequence.

16. Nucleic acid according to claim 15 wherein the linker sequence comprises a nucleic acid sequence encoding at least one glycine residue.

17. Nucleic acid according to either claim 15 or 16 wherein the linker sequence further comprises an N-terminal residue of arginine residue or another destabilising residue.

18. Nucleic acid according to any one of claims 15 to 17 wherein the linker sequence comprises a nucleic acid sequence encoding between 1-1000 residues or between 1-100 or between 1-50 glycine residues.

19. Nucleic acid according to any one of claims 15 to 18 wherein the linker sequence comprises a nucleic acid sequence encoding between 5-35 glycine residues.

20. Nucleic acid according to any one of claims 13 to 19 further including any one or more of the mutations resulting in altered expression of a selected amino acid selected from the group comprising comprising N34A, L31A E2A, L42A, I38A, L7A, F35A, I12A, R14A, V4A, I48A, R9A, L52A, P21A, V49A, R25A, Q26A, R13A, L28A, L39, P21A and A24V.

21. A protein encoded by the vPLB nucleic acid according to any one of claims 13 to 20.

22. A vector comprising the product of any one of claims 9 to 12 or the nucleic acid of any one of claims 13 to 20.

23. A vector according to claim 22 further comprising a promoter for driving expression of the product or nucleic acid.

24. A host cell transformed with the vector of either claim 22 or 23.

25. Use of vPLB nucleic acid according to any one of claims 13 to 20 or the protein encoded thereby as a pharmaceutical.

26. A method of producing vPLB nucleic acid molecule comprising:

(iii) modifying or mutating native or natural PLB so that a region encoding of a methionine residue at the N-terminus of the protein is replaced with an linker sequence comprising a sequence of nucleic acids encoding at least one glycine residue and at least one arginine residue or other destabilising residue at the N-terminus of the vPLB protein; and

(iv) deleting or mutating a region of nucleic acids that encode at least one or both lysine residue(s) from the original PLB sequence so that lysine(s) is/are not expressed in the protein at a location to participate in N-end rule directed ubiquitination.

27. A method according to claim 26 further comprising the step of further modifying the vPLB so as to retain beneficial qualities and to eliminate those considered detrimental.

28. A method according to either claim 26 or 27 further including engineering a mutations resulting in altered expression of a selected amino acid selected from the group comprising comprising N34A, L31A E2A, L42A, I38A, L7A, F35A, I12A, R14A,

V4A, I48A, R9A, L52A, P21A, V49A, R25A, Q26A, R13A, L28A, L39A, P21A and A24V.

29. A method of treating cardiac disorders selected from the group comprising acute congestive heart failure precipitated by mycardial ischemia, hypertrophic cardiomyopathy, dilated cardiomyopathy, which have a common feature of diastolic dysfunction and lethargic Ca^{2+} handling by the SR comprising administering a therapeutically effective amount of vPLB nucleic acid according to any one of claims 13 to 20 or protein encoded thereby or a vector comprising the nucleic acid or a protein expressed by such nucleic acid, to a subject in need of treatment for the specified conditions.